DETAILED ACTION

Claims 1-14 and 20-24 have been cancelled. Claims 15-19 are under examination. Upon further consideration the Examiner has a new grounds of rejection with newly found art. Accordingly, this Action is non-final.

Interview Summary

Please find attached an interview summary. The Examiner thought claim amendments to the route of administration would distinguish the invention over the cited references as the instant claims encompass all routes of administration. This was unacceptable to Applicant and declined. The offer is withdrawn in view of the newly found art.

Withdrawn rejections:

Applicant's amendments and arguments filed 2/12/10 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below is herein withdrawn. Claims 15-19 were rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/53192 (Hereinafter '192) in view of Bedi et al. (Critical Care Medicine 2003, 31, 2470-2477) and Hasselgren et al. (Intensive Care Med 1986, 12, 13-16). This rejection is withdrawn in favor of the rejection(s) to follow.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for *a method of reducing apoptotic cell death in endothelial cells of the intestine in sepsis comprising administering to said a human an effective amount of a pharmaceutical preparation comprising xenon or a xenon gas mixture*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention without an undue amount of experimentation.

Let the Examiner be clear: Applicant is not enabled for *a method of reducing apoptotic cell death in endothelial cells of the intestine in sepsis comprising administering to said a human an effective amount of a pharmaceutical preparation comprising xenon or a xenon gas mixture.*

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: 1) scope or breadth of the claims; 2) nature of the invention; 3) relative level of skill possessed by one of ordinary skill in the art; 4) state of, or the amount of knowledge in, the prior art; 5) level or degree of predictability, or a lack thereof, in the art; 6) amount of guidance or direction provided by the inventor; 7) presence or absence of working examples; and 8) quantity of experimentation required to make and use the claimed

invention based upon the content of the supporting disclosure. When the above factors are weighed, it is the Examiner's position that one skilled in the art could not practice the invention without undue experimentation. While all of the factors have been considered, only those required for a *prima facie* case are set forth below.

1) Scope or breadth of the claims

2) Nature of the invention

The nature of the invention is directed to *a method of reducing apoptotic cell death in endothelial cells of the intestine in sepsis comprising administering to said a human an effective amount of a pharmaceutical preparation comprising xenon or a xenon gas mixture*.

3) Relative level of skill possessed by one of ordinary skill in the art

MPEP 2141.03 states (in part), "A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727, 167 LEd2d 705, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." Id. Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." Id. At 1396, 82 USPQ2d at 1396. The "hypothetical person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art." Ex parte Hiyamizu, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (The Board disagreed with the examiner's definition of one of ordinary skill in the art (a doctorate level engineer or scientist working at least 40 hours per week in semiconductor research or

development), finding that the hypothetical person is not definable by way of credentials, and that the evidence in the application did not support the conclusion that such a person would require a doctorate or equivalent knowledge in science or engineering.).

4) State of, or the amount of knowledge in, the prior art

The sourcebook of models for biomedical research directs one of ordinary skill in the art to the use of animal models in sepsis (pages 473 and 474 of: Sourcebook of Models for Biomedical Research Humana Press; P.Michael Conn Ed.; 2008 New Jersey).

Weber et al. teach that: "In the CLP model signs of apoptosis could be found in thymus, lung and intestinal mucosa and epithelium." (Page 120 of: Cell Apoptosis Research Progress 2008; Robert H. Fenton and Calvin V. Burnside Eds; Nova Science Publishers, Inc., NY). *Note that the endothelium was not included.*

5) Level or degree of predictability, or a lack thereof, in the art

In an animal model of sepsis, Hotchkiss found no evidence of endothelial cell apoptosis in the aorta (Hotchkiss; middle column of page S227 of: Crit Care Med 2002, 30(5), S225-S228). Hotchkiss also report on the different observations of *in vitro* systems that results in contradictory results (page S227, left column). Hotchkiss discloses that: "The role of endothelial cell apoptosis in sepsis remains inconclusive." (page S227, summary). Furthermore, "it is possible that endothelial cell apoptosis may either be beneficial or detrimental to the host." (page S228, left column). The Examiner notes that endothelial cells line the vasculature and are not limited to just the intestine.

Winn et al. (Journal of Thrombosis and haemostasis 2005, 3, 1815-1824) teach: "whether endothelial cell apoptosis occurs in sepsis is somewhat controversial." (page 1819, left column, sepsis).

"Since *in vitro* cell culture models cannot account for "unknown" mechanisms of action, which are detected in live animals (where all the relevant interactions occur), the predictive value of non-animal alternative tests is limited at present." (page 482 of: Risk Assessment of Chemicals: An Introduction Second Edition; C.J. van Leeuwen and T.G. Vermeire Eds. 2007, Springer; Dordrecht, The Netherlands).

Frantz (Nature Reviews Drug Discovery; 2003, 2, page 501) teaches that the use of cell culture and recombinant human cells provide valuable alternatives to animal experiments but these studies still cannot predict the integrated response of a potential drug as accurately as living systems in which a combination of genetic, biochemical, physiological, pathological and environmental influences work in concert (left column).

Anderson et al. (page 743 of: Journal of Antimicrobial Chemotherapy 2008, 62, 738-745) comments on in vitro studies: "…given the exploratory nature of the study, all findings should be considered to be hypothesis generating. Further confirmatory research is needed to understand the mechanisms." And; "…and taken together, our findings provide scientific direction for future research in this area. ***Lastly, as in all in vitro research, we cannot predict how our findings translate into patients.*** The *in vivo* system is many times more complex than *in vitro* conditions…". (Examiner added emphasis).

6) Amount of guidance or direction provided by the inventor

Applicant was required to provide in the specification additional guidance and direction with respect to how use the claimed subject matter in order for the application to be enabled with respect to the full scope of the claimed invention. Although the instant specification discloses that *in vitro* assays of LDH production from cortical neurons and HeLa cells and *in vitro* suppression of caspase 3/7 (Figures 1, 2 and 4 for example), it remains silent on *a method of reducing apoptotic cell death in endothelial cells of the intestine in sepsis comprising administering to said a human an effective amount of a pharmaceutical preparation comprising xenon or a xenon gas mixture*. There exists a vacuum of information between the *in vitro* data taught by Applicant and actually reducing apoptosis in endothelial cells in the intestine in sepsis. The critical teaching that ties the *in vitro* data to intestinal endothelial cell apoptosis in sepsis is missing. Applicant is merely guessing that their *in vitro* data could be extrapolated to a method of reducing apoptotic cell death in endothelial cells of the intestine in sepsis without actually showing anything. In other words, *in vitro* methods can be used to generate ideas and develop hypotheses but cannot be used alone for making broad sweeping assertions about how the *in vitro* results might work in a complex biological system let alone a biological system that is further complicated by a pathological condition (sepsis).

7) Presence or absence of working examples

The specification fails to provide scientific data and working embodiments with respect to *a method of reducing apoptotic cell death in endothelial cells of the intestine in sepsis comprising administering to said a human an effective amount of a pharmaceutical preparation comprising xenon or a xenon gas mixture*. Applicant performed some *in vitro* tests on cortical neurons and HeLa cells in examples 1-4 but not with endothelial cells. ***None of the examples***

were models for apoptosis in sepsis. Applicant merely has a general idea and is assuming that their *in vitro* data can be correlated with reducing endothelial cell apoptosis in the intestine in sepsis. There is no objective evidence that provides the link from Applicant's *in vitro* data to a method of reducing apoptotic cell death in endothelial cells of the intestine in sepsis.

8) Quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure

All Applicant has is a general idea based upon some *in vitro* data with only the intimation that *a method of reducing apoptotic cell death in endothelial cells of the intestine in sepsis comprising administering to said a human an effective amount of a pharmaceutical preparation comprising xenon or a xenon gas mixture* can work. Applicant has not shown any data concerning endothelial cell apoptosis and expects a leap of faith without providing a bridge of logic that the instant method would have any reduction of endothelial apoptotic cell death in sepsis. This is especially true when the art, Hotchkiss, whom actually performed experiments on an animal model of sepsis in contrast to Applicant, and did not find any sign of endothelial cell apoptosis in the aorta and the art. The art is not even sure if endothelial cells undergo apoptosis during sepsis! How is the method supposed to work when it is not yet certain that endothelial cells undergo apoptosis in sepsis? In other words, there is no method if the endothelial cells do not undergo apoptosis in sepsis. Furthermore, Anderson et al. teach how *in vitro* testing cannot predict responses *in vivo*. For all intents and purposes, Applicant has left it to one of ordinary skill in the art to figure out if endothelial cells undergo apoptosis in sepsis and if xenon will have any effect in reducing that. Essentially, the artisan has to figure out how to do this themselves. As a result, one of ordinary skill in the art would be required to conduct an undue amount of

experimentation to determine if endothelial cells have reduced apoptosis in the intestine in sepsis in the method instantly claimed.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." (Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997)).

The enablement requirement is not satisfied.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Finley et al. (Surgery, 1975, 78(1), 87-94) teach methods of injecting ^{133}xenon dissolved in saline solution into patients with sepsis (page 87, right column and page 88, lower right column and Discussion page 92). Please note that this reference is not being applied against the instant claims based upon inherency because of the enablement problem above but may be applied in the future if the enablement rejection is overcome.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERNST V. ARNOLD whose telephone number is (571)272-8509. The examiner can normally be reached on M-F 7:15-4:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ernst V Arnold/
Primary Examiner, Art Unit 1616